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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

WALICKA, MALGORZATA A

ART UNIT PAPER NUMBER

1652

DATE MAILED: 11/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/423,554

Applicant(s)

ARISTIDOU ET AL.

Examiner

Malgorzata A. Walicka

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 07 September 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 25, 26, 43, 45, 46 and 69-73 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 25 and 26 is/are allowed.
- 6) ☒ Claim(s) 43, 45, 46, and 69-73 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |                                                                                                                        |                                                                                         |
|------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                                                       | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____                                                |

The Amendment filed on Sept. 7, 2005 comprising amendments to the claims is acknowledged. Claims 1-24 and 27- 42, 44, 47-68 are canceled; new claims 69-73 are entered. Claims 43, 45 and 46 and 57 have been amended. Claims 25, 26, 43, 45, 46, 69-73 are pending, and under examination.

### **Detailed Office Action**

#### **1. REJECTIONS**

##### ***1.1. 35 USC 112, second paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

New claim 72 and 73 recite the limitation "a yeast strain" in the first line. There is insufficient antecedent basis for this limitation in the claim. The base claim 43 does not recite as a host microorganism yeast.

Claims 72 and 73 are improperly dependent because they broaden the scope of the base claim 43. Claim 43 is directed to a method of use a transformant belonging to any species of *Saccharomyces* and *Schizosaccharomyces* and not from any yeast.

##### ***1.2. 35 USC 112, first paragraph***

###### **1.2.1. Lack of written description**

Rejection of claims 49, 57, 60, 61 and 67-68 made in the Office Action of March 9, 2005 (previous Action) is moot because the claims have been canceled. Rejection of

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claim 46 for lack of written description of carbohydrates is withdrawn in the light of Applicants arguments.

Claim 43, 45, 46 and 69-71 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a method of increasing the yield of production of ethanol wherein the method comprises as the first step transforming a host microorganism selected from group consisting of *Saccharomyces* spp. and *Schizosaccharomyces* spp. with one or more polynucleotides encoding an enzyme selected from the group consisting of NAD-dependent glutamate dehydrogenase, and malic enzyme.

Regarding NAD-dependent glutamate dehydrogenase, the claims are directed to genus of methods which lack written description in the disclosure. The specification does not teach that introduction of NAD-dependent GDH to wild type *S. cerevisiae* H1346 increases production of ethanol. Applicants have shown the **increase in ethanol production related to introduction of glutamate dehydrogenase gene only for two transformants,**

H1803 (*S. cerevisiae* + XR + XDH + XK + **GDH**), Fig. 4, and

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H1791 (*S. cerevisiae* + XR + XDH + **mGDH**), Table 1, as compared to their controls (*S. cerevisiae* + XR + XDH + XK ) and (*S. cerevisiae* + XR + XDH). Providing the two transformants with a particular set of genes, which after transfection with NAD-dependent GDH produce more ethanol than the initial *S. cerevisiae* transformant does not identify the whole genus of *Saccharomyces* and *Schizosaccharomyces* transformants in which the production of ethanol is higher than in their counterparts who do not contain NAD-glutamate dehydrogenase gene. Applicants do not teach any *Schizosaccharomyces* species which after transformation with NAD-dependent GDH produce more ethanol than the initial host organism. Applicants' basic yeast cells that are used as control in examining the yield of ethanol production are integrants comprising xylose reductase (XR) and xylitol dehydrogenase (XGH) genes of *Pichia stipitis* (XYL1 and XYL2); see Example 1. Applicants do not teach any other *Saccharomyces* host that after transfecting with NAD-glutamate reductase produced more ethanol than before transformation.

Regarding malic acid, Applicants failed to show the increase in production of ethanol by a wild type *Saccharomyces* sp. or wild type *Schizosaccharomyces* transformed with a gene encoding malic enzyme. The only transformant H2193, i.e., H1346+ MAE, i.e. wild type plus malic enzyme, is not shown to produce more ethanol than the wild type. Applicants teach only **three transformants** of *S. cerevisiae* transformed with **malic enzyme (ME)** having higher production of ethanol than the transformant, which does not overexpress ME. Transformant H2193 (*S. cerevisiae* + XR + XDH + mME) as compared to (*S. cerevisiae* + XR + XDH), growing on glucose (Table

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3) xylose and transformant H2195 (*S. cerevisiae* + XR + XDH), growing on xylose; see Fig. 9. However, the statistical significance of the measurement is uncertain in this case. In case of H2222 (*S. cerevisiae* + XR + XDH + XK +m **ME**) growing on xylose, the increase in production of ethanol, Fig. 10, and was substantial. Applicants also teach *S. pombe* transformant H2369 (*S. pombe* +XR+XDH +mME) which produces more alcohol than (*S. pombe* +XR+XDH); see Fig. 14.

Providing evidence that two transformants of *S. cerevisiae* transformed with particular set of genes and NAD-dependent GDH or ME as well as three transformants of *S. cerevisiae* comprising the same set of genes plus ME gene, and providing evidence that one *S. pombe* transformant having particular set of genes plus ME gene produce more ethanol than their not transformed counterparts, does not provide identifying characteristics of all transformants of any *Saccharomyces* and *Schizosaccharomyces* sp. that produce more ethanol after transformation with NAD-dependent GDH or ME than their not transformed counterparts.

In conclusion, claim(s) 43, 45, 46, and 69-71 are rejected because they contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had the possession of the claimed invention.

**Response to Applicants traverse.**

In their Remarks, on page 9, Applicants refer to the list of transformants presented on page 8-9 of the Remarks, and state, "A review of the above reveals that

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there are disclosed embodiments which produce a product but do not have either xylose reductase (XR) or xylitol dehydrogenase (XDH). Thus claim 43 is so limited".

Applicants' argument is not persuasive for two reasons.

1. Claim 43 is not directed to a method for production of ethanol, but to a method for **increasing yield of ethanol produced**. Applicants seem not to remember about this important language of preamble.

2. Applicants invention was to make yeast transformants capable of growing on xylose, and for that reason they had to contain XR and XDH; see the specification, page 1, line 25-26 and line 32 and further. Containing XR and XDH genes did not, however lead to an efficient production of ethanol in yeast transformants growing on xylose, thus further transformation with another gene, NAD-dependent GDH or ME, was necessary.

### 3.2.2. Scope of enablement

Rejection of claims 49, 57, 60, 61 and 67-68 made in the Office Action of March 9, 2005 (previous Action) is moot because the claims have been canceled. Rejection of claim 46 for lack of written description of carbohydrates is withdrawn in the light of Applicants arguments.

Claims 43, 45, 46 and 69-71 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for transformants H1803 (S. cerevisiae + XR + XDH + XK + **GDH**), H1791 (S. cerevisiae + XR + XDH + **mGDH**), H2195 (S. cerevisiae + XR + XDH + mME), H2222 (S. cerevisiae + XR + XDH + XK + **mME**) and

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H2369 (S. pombe +XR+XDH +mME) that produce more ethanol than their counterparts not comprising GDH or ME, does not reasonably provide enablement for any *Saccharomyces* or *Schizosaccharomyces* sp. transformed with NAD-dependent GDH or malic enzyme that after transformation produce more ethanol.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Otherwise, undue experimentation is necessary to make the claimed invention.

Factors to be considered in determining whether undue experimentation is required are summarized *In re Wands* [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claimed invention encompasses transformation of any species of *Saccharomyces* or *Schizosaccharomyces* wild type, naturally occurring mutants as well as any mutants and transformants man-made, i.e. the scope comprises all natural or man-made *Saccharomyces* and *Schizosaccharomyces* species strains, with a gene selected from genes encoding

- a) glutamate dehydrogenase,
- b) malic enzyme,



Wherein after transformation production of ethanol is higher than before transformation.

Although the art of genetic engineering of yeast cells used for production of ethanol is well developed and skills of artisans high, the specification fails to provide enough guidance as to how to make the claimed transformant, because expressing or overexpressing the genes encoding a)-b) does not always results in an increase of ethanol production. In summary, result of transformation will be a combination of the intricacies of the metabolism of the yeast cell selected for transformation and activity of the enzymes encoded by the transformed genes. Only the combination of the genetic set of parental cell used for transformation and the NAD-dependent glutamate dehydrogenase or malic enzyme may ensure that transformation will lead to the desired result of increasing ethanol production. Providing the above listed transformants obtained from specific host does not provide sufficient guidance, thus one having skills in the art is forced to experimentation which is out of routine. In conclusion, without further guidance on the part of Applicants regarding the parental cell to be transformed probability of making the invention is low, and the experimentation left to those skilled in the art is extensive and undue

## **2. Conclusion**

All claims are rejected. Applicants are reminded about allowable subject matter stated in previous Office Actions.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka whose telephone number is (571) 272-0944. The examiner can normally be reached on Monday-Friday from 10:00 a.m. to 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

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Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Malgorzata A. Walicka, Ph.D.

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Patent Examiner

A handwritten signature in black ink, appearing to read 'P. Achur' or similar, with a long horizontal stroke extending to the right.

PONNATHAPUACHUTAMURTHY  
SUPERVISORY PATENT EXAMINER  
TECHNOLOGY CENTER 1000